REMARKS

The Office Action of March 17, 2009, has been carefully studied. Claims 1-7, 9-21, 23-26, and 28-30 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

Interview Summary

Applicant's attorney wishes to thank Examiner Sackey for the courtesies extended during the telephone interview of May 12, 2009. During that interview it was agreed that there was support in the specification for specific conditions and diseases for which there were examples. Accordingly, claims 29 and 30 have has been submitted to recite these specific diseases and conditions.

Amendments to the Claims

The claims have been amended to recite methods for treating an animal suffering from a disease or condition resulting oxidative or nitrosative stress, and claims 29 and 30 have been submitted to recite that the said disease or condition is selected from the group consisting of hypotension, vasoplegia, vasoconstriction, vasorelaxation,

thrombosis, blood clotting, endotoxic shock and septic shock. Support for this amendment and newly submitted claims can be found in the specification as filed at paragraphs 0108-0123.

Rejections under 35 U.S.C. 112

Claims 1-7, 9-14, 21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

This rejection is respectfully traversed. Claims 29 and 30 have been presented to recite that the treatment is for treating specific disease or conditions resulting from oxidative or nitrosative stress. Specific examples of diseases caused by oxidative or nitrosative stress, as described in the specification and as claimed herein, include hypotension, vasoplegia, vasoconstriction, vasorelaxation, thrombosis, blood clotting, endotoxic shock and septic shock. It is clear from the specification that the mechanisms of treating these conditions with perfluorocarbons is well described so that one skilled in the art, without undue experimentation, can readily practice the invention.

Figure 1A, descried in paragraph 0108, shows that 1% v/v perfluorocarbon saturated with NO increases the rate of S-nitrosoglutathione formation more than 20-fold *in vitro*. This effect was even greater at a lower dose of perfluorocarbon *in vivo*. This demonstrates that uncoupling of NO-donors

formation from overall NO synthesis provides a means to control blood pressure and organ profusion. The perfluorocarbons can thus be administered to regulate blood pressure and blood clotting.

Figures 4A and 4B, and paragraphs 0110-113 demonstrate the use of perfluorocarbons to increase blood pressure, i.e. to treat hypotension.

Paragraph 0016 notes that to increase blood flow one can administer >1% perfluorocarbon. To decrease blood pressure to a steady level, one would administer 0.5% or less perfluorocarbon with a low molecular weight nucleopphile. Under these conditions, a relatively small increase in plasma nucleophile, such as a low molecule weight thiol, would have a great stimulating effect on vasodilatory S-nitrosothiol production, as shown in Figures 6A and 6B.

Paragraph 0117 describes treating inflammation or sepsis, including septic shock and endotoxic shock, specifically by sequestering circulating NO without suppressing NOX activities, making the perfluorocarbons useful in attenuating hypotension and vasoplegia during septic shock.

Figure 7 and paragraph 0118 describe how administration of small concentrations of perfluorocarbons can act as a powerful vasodilator. This effect is due to micellar catalysis of vasoactive S-nitrosothiol formation by

perfluorocarbons, as shown in Figures 3, 5 and 6. *In vivo* and *in vitro* results shown in Figures 7 and 8 support α-lipoic acid acting as a shuttle to transfer NO^+ from the interior of the fluorocarbon micelles to outside hydrophilic low molecular weight RSH, thus potentiating perfluorocarbon-mediated RS-NO formation. Thus, the perfluorocarbons are potent vasodilators and anticoagulants.

Paragraphs 0121-0123 describe a study to demonstrate the use of perfluorocarbons in treating endotoxic shock in rats. As shown in Figure 10B, survival of the animals after 24 hours was increased six-fold in comparison with control and HE S groups, respectively.

It is respectfully submitted that numerous *in vitro* and *in vivo* examples have been provided in the present specification. Specifically, paragraph 0114 describes the ability of perfluorocarbons to catalyze S-nitrosothiol formation *in vivo* and to confirm its relation to perfluorocarbon-induced vasorelaxation.

Submitted herewith is a copy of Apel et al., *Annu. Rev. Plant Viol.* **204(55)** 373-399, 2004, which describes the mechanisms of oxidative stress. It is clear from this review article that those skilled in the art are conversant with oxidative stress and methods for reducing it, as well as the cell damage that can be caused by oxidative stress.

As the Examiner is well aware from MPEP Section 2107.03, evidence of pharmacological or biological activity of a compound is relevant to a therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility, *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 225 USPQ 885 (CCPA 1980); *Nelson v. Bowler* 626 F.2d 853, 206 USPQ 881 (CCPA 1980). This reasonable correlation can be established by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals) or by any combination thereof. The applicant need not prove the correlation between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does applicant have to provide actual evidence of success in treating humans. Instead, the courts have held that all that is required is a reasonable correlation between the activity and the asserted use.

Applicant has demonstrated a direct correlation between administering perfluorocarbons and the effects on oxidative and nitrosative stress. Articles from scientific journals have been submitted to demonstrate the relationship between oxidative and nitrosative stress and a variety of medical conditions.

The test for enablement, that is, whether a particular claim is supported by the disclosure, is a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims to enable one skilled in the art to make and use the claimed invention. The standard used is whether the experimentation required to use the invention is undue or unreasonable, *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). See also, *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8USPQ 2d 1217, 1223 (Fed. Cir. 1099), "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."

The specification has provided a number of examples of treating diseases or conditions related to oxidative or nitrosative stress, and applicant has submitted articles from scientific journals to confirm the types of diseases and conditions caused by oxidative and nitrosative stress. One skilled in the art, reading the specification in light of what was known at the item the application was filed, would be able to treat disease or conditions resulting from oxidative or nitrosative stress without undue experimentation.

Claims 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 has been cancelled, so this rejection is moot with respect to claim 22.

With respect to claim 21, it is respectfully submitted that the specification as filed is replete with examples of using perfluorocarbons to treat animals suffering from conditions resulting from nitrosative stress, *i.e.*, conditions resulting from the presence of excess or insufficient NO. The metes and bounds of "nitrosative stress" are well described in the present specification and in the literature. Accordingly, one skilled in the art would be able, without undue experimentation, to determine if a patient had a disease or condition resulting from nitrosative stress and would understand from the specification as filed how to treat this patient.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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